Official Protocol Title:	A Gluten Challenge Study to Characterize Peripheral Blood and Intestinal Gluten-specific CD4+ T cell Subsets in Patients With Celiac Disease
NCT number:	NCT04054544
Document Date:	17-Jul-2020

Title Page

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., NJ, U.S.A. (MSD).

Protocol Title: A Gluten Challenge Study to Characterize Peripheral Blood and Intestinal Gluten-specific CD4+ T cell Subsets in Patients With Celiac Disease

Protocol Number: 402-05

Compound Number: MK-0000

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

Approval Date: 17 July 2020

Sponsor Signatory

Typed Name: Date
Title:

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Date
Title:

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment -05	17-Jul-2020	To ensure participant safety, COVID-19 testing was added to the screening visit and prior to the duodenal biopsy procedure.
Amendment -04	18-Jun-2020	The main rationale for Amendment 04 is to remove the restriction that leftover PBMC samples will only be retained if initial samples for ELISPOT analysis have insufficient signal for assay development.
Amendment -03	13-Apr-2020	To ensure participant safety, Exclusion Criterion #9 was revised to exclude participants on Coumadin™ or any anticoagulants.
Amendment -02	25-Oct-2019	The Secondary Objective was moved to be an Exploratory Objective.
Amendment -01	16-Aug-2019	The main rationale for Amendment 01 is reprioritization of study objectives and some changes in participant entry criteria.
Original Protocol	30-Apr-2019	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

To ensure participant safety, COVID-19 testing was added to the screening visit and prior to the duodenal biopsy procedure.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities 10.2 Appendix 2: Clinical Laboratory Tests	Added COVID-19 testing.	Due to global COVID-19 restrictions, COVID-19 testing was added to the screening visit and prior to the duodenal biopsy procedure to ensure participant safety.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Gluten Challenge Study to Characterize Peripheral Blood and Intestinal Gluten-specific CD4+ T cell Subsets in Patients With Celiac Disease

Short Title: Gluten Challenge Study in Celiac Disease Patients

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in male and female participants with celiac disease.

Primary Objectives	Primary Endpoints
- To determine the phenotypes of gliadin peptide/HLA-DQ2 multimer-positive CD4+ T cell subsets in the peripheral blood before and after gluten challenge and from duodenal biopsies after gluten challenge. Estimation: The percentages of α-gliadin and ω-gliadin-reactive CD4+ T cells expressing known activation and inhibitory receptors (including but not limited to: CD25 (IL-2R), CD95 (Fas), CD279 (PD-1), TGFβ1R, and IL-27R) will be estimated.	- α-gliadin and ω-gliadin-reactive CD4+ T cells

Overall Design:

Study Phase	Early Phase 1
Primary Purpose	Basic Science
Indication	Celiac Disease
Population	Participants with celiac disease
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded Open-label
Masking	No Masking
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 12 months from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 15 participants will be allocated/randomized such that 15 evaluable participants complete the study as described in Section 9.9.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Intervention</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin.</th><th>Regimen/ Treatment Period</th><th>Use</th></tr>
<tr><td>All participants</td><td>Gluten</td><td>4 g</td><td>Twice daily</td><td>Oral</td><td>Daily for 13 days</td><td>Challenge agent</td></tr>
</table>
</td></tr>
<tr><td>Total Number</td><td>1</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 8 weeks from the time the participant signs the Informed Consent Form through the final contact. After a screening period of up to 28 days, each participant will be receiving assigned intervention for 13 days. After the end of treatment each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

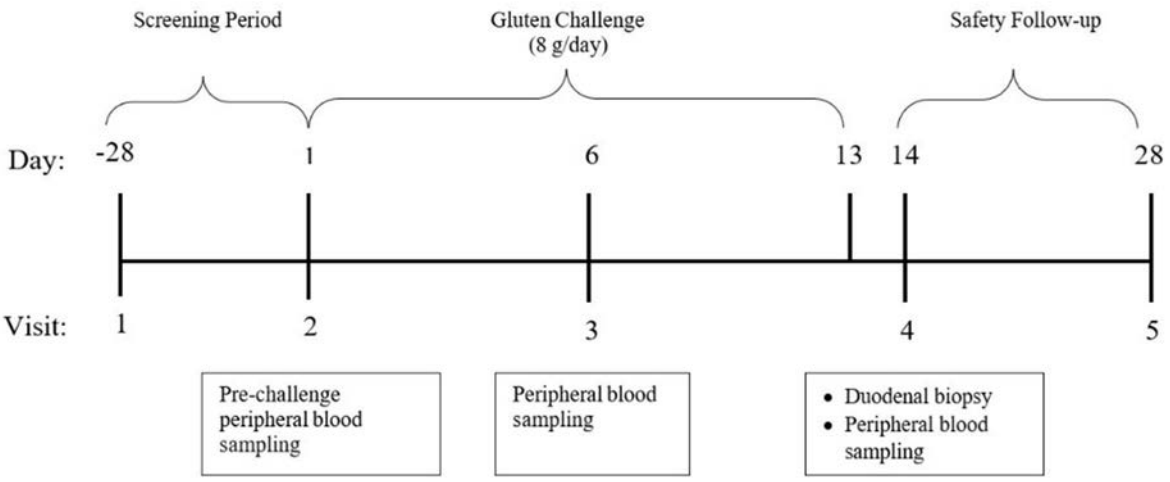

Figure 1 Study Diagram

1.3 Schedule of Activities (SoA)

	All Panels/Periods							
Study Period	Screening	Pre-dose	Intervention				Post-study	Notes
Scheduled Day	Screening (up to -28 days)	Day 1 Pre-dose	Day 1	Day 6	Day 13	Day 14 (+/- 1 day)	Post-study (14 days after last gluten administration)	
Administrative Procedures								
Informed Consent	X							
Informed Consent for Future Biomedical Research	X							
Assignment of Screening Number	X							
Participant Identification Card	X							
Inclusion/Exclusion Criteria	X	X						Recheck clinical status before start of gluten challenge
Medical History	X							Includes usage of drugs, alcohol, and tobacco
Prior/Concomitant Medication Review	X	X	X	X		X	X	
Assignment of Treatment/Randomization Number		X						
Gluten Administration/Dispensing			X----------X					Gluten will be administered daily from Day 1 to Day 13. In the event that Day 14 procedures are conducted on Day 13, gluten intended for Day 13 will not be consumed.
Participant Gluten Consumption Log			X----------X					Participants will complete this log daily.
Safety Procedures								
Full physical examination	X	X				X		Pre-dose will be targeted PE
Height	X							
Weight	X	X				X	X	
Vital Signs (BP, HR, RR)	X	X				X	X	

	All Panels/Periods							
Study Period	Screening	Pre-dose	Intervention				Post-study	Notes
Scheduled Day	Screening (up to -28 days)	Day 1 Pre-dose	Day 1	Day 6	Day 13	Day 14 (+/- 1 day)	Post-study (14 days after last gluten administration)	
Body Temperature	X	X				X	X	
12-lead ECG	X							
Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X							
Urine β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)		X				X		
Serum FSH - (postmenopausal women only)	X							
Blood for HLA Genotyping for Celiac Disease	X							Results from previous testing may be used in lieu of genotyping at screening
Anti-tTg, HIV, hepatitis B and C screen	X							
UDS	X							Screening UDS is mandatory, any additional UDS are conducted per site SOP
COVID-19 Testing	X					X		COVID-19 nasal swab test or blood test, per local practice, if deemed possible/allowed based on test capacity, and according to local health practice. Testing prior to the Day 14 duodenal biopsy may be done within 2 to 3 days prior to the procedure per the investigator's discretion. Result must be negative for duodenal biopsy to be performed.
Hematology	X					X		
Urinalysis	X					X		

	All Panels/Periods							
Study Period	Screening	Pre-dose	Intervention				Post-study	Notes
Scheduled Day	Screening (up to -28 days)	Day 1 Pre-dose	Day 1	Day 6	Day 13	Day 14 (+/- 1 day)	Post-study (14 days after last gluten administration)	
Chemistry	X					X		
CDSD	X	X----------X						Participants will complete the CDSD daily.
AE/SAE review	X	X	X	X	X	X	X	
Pharmacodynamics								
Blood for Serum Cytokine/Chemokine Assay		X		X		X		
Blood for PBMC		X		X		X		
Duodenal Biopsy						X		
Biomarkers								
Blood for Genetic Analysis		X						Collect predose from enrolled participants only – See Section 8.8

AE=adverse event; BP=blood pressure; CDSD=Celiac Disease Symptom Diary; ECG=electrocardiogram; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HLA=human lymphocyte antigen; HR=heart rate; PBMC=peripheral blood mononuclear cells; PE=physical examination; RR=respiratory rate; SAE=serious adverse event; UDS=urine drug screen; WOCBP=women of childbearing potential

2 INTRODUCTION

2.1 Study Rationale

The objective of this experimental medicine study is to profile cell surface receptors on blood and intestinal gluten-specific CD4+ cells from patients with CeD to inform the development of novel therapies for celiac disease.

2.2 Background

Celiac disease is an enteropathy of the small intestine triggered by ingestion of gluten present in wheat (gliadin), rye (secalin), and barley (hordein). It is one of the most common immune-mediated diseases, affecting an estimated 10 million people globally, with a prevalence of 0.5-1% which is predicted to increase over time. It is a malabsorptive disease characterized by GI symptoms (diarrhea, weight loss) and vitamin deficiencies (iron, vitamin D), leading to anemia and osteoporosis. CeD is diagnosed by the presence of antibodies to tTG and characteristic pathologic changes on duodenal biopsies. The only current management option for CeD is strict, lifelong adherence to a GFD; however, unintentional exposure to gluten through food contamination is common, which may lead to persistent disease over time. In addition, gluten-free food options can be scarce, expensive, and low in key nutrients, and patient anxiety in social situations involving food is common. There is a high unmet need for CeD treatments beyond GFD, and multiple agents are being studied for the treatment of CeD in Phase 2 clinical trials, targeting both immune- and non-immune mediated mechanisms [Wungjiranirun, M., et al 2016].

Proline-rich gliadin peptides derived from gluten are deamidated in intestinal submucosa by type 2 tTG, which then bind with high affinity to HLA-DQ2.5/DQ8 (~90%/~10% CeD patients, respectively) on antigen presenting cells. These HLA-gliadin complexes bind to specific gluten-specific T cell receptors expressed by CD4+ T cells in the lamina propria, differentiating them towards a pro-inflammatory Th1 phenotype, producing cytokines such as IFN-γ, IL-21, and TNFα. Within the inflammatory lesion, B cells act as antigen presenting cells (APCs) for gliadin-specific T cells and differentiate into plasma cells producing high affinity anti-TTG Abs, whose pathogenic significance are not clear, but function as a biomarker for disease diagnosis and recent gluten exposure. Activated intraepithelial CD8 T cells induce further mucosal damage [Jabri, B. 2017].

The HLA-DQ2.5 restricted, gluten-specific Th1 response in CeD is largely driven by a few overlapping immunodominant gliadin peptides. Multiple studies have confirmed α-gliadin 57-73 (Q65E) as a dominant T cell epitope in CeD [Anderson, R. P., et al 2000]. A follow up epitope mapping study systematically profiled gliadin peptide libraries consisting of over 2500 20-aa oligopeptides and identified ω-gliadin W03-E7 as an additional immunodominant peptide [Tye-Din, J. A., et al 2010]. Regulatory T cells (Tregs) play an important role in maintaining immune tolerance. Treg subsets, including FOXP3+ Tregs (CD4+CD25+IL-127^{low}) and IL-10 producing Tr1 T cells (CD4+CD49b+LAG3+), can be generated in vitro and are being studied in cellular therapy clinical trials for organ transplantation and T1DM.

2.3 Benefit/Risk Assessment

Participants in this clinical study will not receive direct benefit from participation.

Risks anticipated for participants in this trial are those related to the gluten challenge, venipuncture and biopsy procedures.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

This study is to be conducted in male and female participants with celiac disease.

Objectives	Endpoints
Primary	
• To determine the phenotypes of gliadin peptide/HLA-DQ2 multimer-positive CD4+ T cell subsets in the peripheral blood before and after gluten challenge and from duodenal biopsies after gluten challenge. Estimation: The percentages of α-gliadin and ω-gliadin-reactive CD4+ T cells expressing known activation and inhibitory receptors (including but not limited to: CD25 (IL-2R), CD95 (Fas), CD279 (PD-1), TGFβ1R, and IL-27R) will be estimated.	• α-gliadin and ω-gliadin-reactive CD4+ T cells
Secondary	
• None	
Exploratory	
• To estimate the frequency, phenotype, and function of effector IFN-γ-producing gluten-specific CD4+ T cells (Teff) in the peripheral blood before and after gluten challenge.	• effector IFN-γ-producing gluten-specific CD4+ T cells (Teff)

Objectives	Endpoints
• To characterize individual single-cell gene expression to define T cell receptor sequences as well as novel activation and inhibitory receptors in blood (pre- and post-gluten challenge) and post-gluten challenge duodenal biopsies using single cell RNA sequencing (scRNA-Seq).	• single cell RNA sequencing (scRNA-Seq).
• To determine the relationship between severity of histologic damage on duodenal biopsy, celiac disease symptoms, and the quantity and quality of gluten-specific CD4+ T cell responses after gluten challenge.	• Histology, CDSD, gluten-specific CD4+ T cells
• To estimate the frequency, phenotype, and function of blood and duodenal gluten-specific CD4+ regulatory T cells (Treg) induced after in vitro treatment with experimental compounds.	• gluten-specific CD4+ regulatory T cells (Treg)
• To estimate the frequency, phenotype, and function of effector IFN-γ-producing gluten-specific CD4+ T cells (Teff) after in vitro treatment with experimental compounds.	• effector IFN-γ-producing gluten-specific CD4+ T cells (Teff)
• To estimate the levels of cytokines and chemokines in serum before and after gluten challenge	• Serum cytokines and chemokines
• To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in this study.	• Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a multi-site, open-label gluten challenge study to characterize peripheral blood and intestinal gluten-specific CD4+ T cell subsets in patients with CeD. Participants will receive 8 g gluten daily for 13 consecutive days. Blood samples will be taken at pre-dose, Day 6, and Day 14. Duodenal biopsy samples will also be collected on Day 14. Participants will complete a symptom diary as described in the SoA.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

Because it is a Phase 1 assessment of a gluten challenge in humans, and the pharmacodynamic and safety profiles of a gluten challenge are being evaluated, this protocol is written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modification permitted within the protocol parameters.

4.2 Scientific Rationale for Study Design

Gliadin-specific CD4+ T cells are infrequent in the blood above background staining by flow cytometry in patients with CeD on a GFD [Raki, M., et al 2007]. Gliadin-specific CD4+ T cells may be identified by flow cytometry using MHC-gliadin tetramers. After the first three days of a gluten challenge, gliadin-specific T cells are detectable in the blood on day 6 after initial challenge and can therefore be readily identified [Raki, M., et al 2007]. Gliadin peptide mixtures can stimulate an IFN-γ enzyme-linked immunospot (ELISPOT) response from peripheral blood T cells after gluten challenge [Tye-Din, J. A., et al 2010]. Gliadin-specific T cells may also be isolated at ~10-100x higher frequencies from duodenal biopsies after gluten challenge [Bodd, M., et al 2013]. A traditional gluten challenge used in clinical practice for the diagnosis of CeD may last from 2 to 8 weeks. A biomarker study assessing histologic responses at 3 and 14 days after gluten challenge determined that histologic changes were more pronounced at 14 days at both dosage levels [Leffler, D., et al 2013]; therefore, a 13 day gluten challenge is proposed in order to maximize the feasibility of obtaining immune cells in the blood and duodenum on Day 14, as well as to adequately replicate the inflammatory milieu for scRNA-Seq analysis. Polyclonal gliadin-specific T cell cultures and monoclonal gliadin-specific T cell lines from patients will also be generated for long-term use in the laboratory using established protocols. These assays will be utilized to analyze gliadin-specific T cells from patients after gluten challenge.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of gluten administration and procedures during this study will be evaluated by clinical assessment of adverse experiences and other safety measurements. Summary statistics for laboratory safety tests and/or vital signs may also be computed, as deemed clinically appropriate.

4.2.1.2 Pharmacodynamic Endpoints

Patient responses to gluten challenge will be monitored by symptom assessment using the CDSD and by histologic scoring of duodenal biopsies.

4.2.1.3 Planned Exploratory Biomarker Research

4.2.1.3.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.4 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use

such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research are presented in Appendix 6.

4.3 Justification for Dose

A biomarker study assessing histologic responses at 3 and 14 days after both low-dose (3 g/day) and high-dose (7.5 g/day) gluten challenges determined that histologic changes were more pronounced at 14 days at both dosage levels [Leffler, D., et al 2013]. Another biomarker study determined that a 5.7 g/day gluten challenge administered over 14 days resulted in significant increases in circulating gluten-specific T cells and intraepithelial lymphocytes on duodenal biopsy, but did not fully establish significant mucosal architectural changes in the majority of patients [Sarna, V. K., et al 2018]. An 8 g/day, 13-day gluten challenge is proposed in order to maximize the feasibility of obtaining immune cells in the blood and duodenum and to replicate the inflammatory milieu for scRNA-Seq analysis.

As this is a Phase 1 assessment of a gluten challenge in humans, and the pharmacodynamic and safety profiles of a gluten challenge are being evaluated, modifications to the dosing regimen or study procedures may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. The overall study end will then not be identified until the Sponsor has made the decision to end the study following this review period. The Competent Authority(ies) and Institutional Review Board(s)/Independent Ethics Committee(s) [IRB(s)/IEC(s)] will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

Male/Female participants with biopsy-proven CeD between the ages of 18 and 70 years (inclusive) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

1. Participant must have documented diagnosis with CeD by duodenal/jejunal biopsy at least 6 months prior to entrance into the study.

2. Participant must be on a GFD for at least the past 12 months.

Demographics

3. Participant is male or female.

4. Participant is from 18 years to 70 years of age inclusive, at the time of signing the informed consent.

Female Participants

5. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a WOCBP

     OR

   - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

   - Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

   - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

6. The participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study. The participant may also provide consent/assent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Diagnostic Assessments

7. Must be HLA-DQ2.5 positive, assessed at screening. If participants have already been genotyped, results from previous testing may be used in lieu of genotyping at screening.

8. Has anti-tTG <2x ULN as measured by serology.

Medical Condition

9. Be judged to be in good health based on medical history, physical examination (including a targeted neurological exam), VS measurements and ECG performed prior to treatment allocation.

10. Have a BMI 18-35 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height $(m)^2$.

Other Inclusions

11. Have a negative urinary screen for illicit drugs at screening.

12. Understands study procedures and is willing to comply with trial restrictions (see Section 5.3 for a summary of trial restrictions).

13. Be judged to be in good health based on laboratory safety tests obtained at screening. Appendix 2 provides a table of laboratory safety tests to be performed, and Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has any chronic active GI disease (eg, clinically active CeD despite being on GFD for past 12 months, Crohn's disease, ulcerative colitis, lymphocytic colitis). Inactive, stable/well-treated lactose intolerance, FODMAP intolerance, GERD, and IBS are allowed.

2. Has clinically active endocrine, gastrointestinal (other than CeD), cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases. Participants with a remote history of uncomplicated medical events or stable medical diseases with no symptoms and stable treatment for the past >3 months may be enrolled in the study at the discretion of the investigator.

3. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder within the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

4. Participant has an eGFR ≤80 mL/min/1.73 m^2 at the screening visit based on the Cockcroft-Gault (CG) equation below:

   Cockcroft-Gault Equation:

   $$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt [kg]})}{(72)(\text{serum creat [mg/dL]})}$$

   When creatinine is measured in micromole/litre, use this formula:

   $$Cl_{Cr} = \frac{(140\text{-age[yr]})(\text{body wt[kg]})}{(72)(\text{serum creatinine [micromol/L] x 0.0113})}$$

   For females, multiple the result by 0.85.

   At the discretion of the investigator a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the creatinine clearance.

   Participants who have a measured creatinine clearance of up to 10% below 80 mL/min may be enrolled in the study at the discretion of the investigator.

5. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or systemic allergic reaction to prescription or non-prescription drugs or food.

6. Subject has a history of severe acute symptomatic reactions to sporadic gluten ingestion.

7. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

8. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

9. Is on Coumadin™ or other anticoagulants.

10. Is unable to refrain from or anticipates the use of systemic anti-inflammatory, immunosuppressive, or immunomodulatory medications, which may include ibuprofen > 2400 mg/day, naproxen >750 mg/day, prednisone >10 mg/day, or methylprednisolone > 8 mg/day, within 48 hours prior to the start of and throughout the entire gluten challenge.

Prior/Concurrent Clinical Study Experience

11. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

12. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

13. Is under the age of legal consent.

14. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator. All alcoholic beverages must be gluten free.

15. Is a regular user of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 6 months. Participants must have a negative UDS at screening.

16. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

17. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Diet Restrictions

Participants will be required to fast at least 8 hours (may be longer if required per site SOP) prior to the duodenal biopsy procedure.

The gluten may be consumed with or without a meal.

5.3.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the prestudy and poststudy visits. On blood sampling days (ie, Days 1, 6, and 14) participants will refrain from consumption of alcohol 24 hours prior to reporting to the CRU and after departing the CRU.

On intermediate days and at all other times, alcohol consumption is limited to no more than approximately 3 gluten-free alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the prestudy (screening) visit, throughout the study, and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information may be included, as outlined in the electronic case report forms (eCRF) entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention or withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Each participant will receive study intervention (gluten) at Visit 2 and is to take the first dose that same day. The participant should consume the intervention (gluten) daily for 13 days.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in [Table 1].

Table 1 Study Interventions

Intervention Name	Type	Dose Formulation	Dosage Level	Route of Administration	Regimen/Treatment Period	Use	IMP/NIMP	Sourcing
Gluten Challenge	Dietary substance	Powder	4 g	Oral	BID for 13 consecutive days	Challenge agent	NIMP	Locally
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.								

All supplies indicated in [Table 1] will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants in this study will be allocated by nonrandom assignment.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management. See Section 7.1 for the compliance threshold requiring discontinuation.

Study participants will complete a gluten consumption log to record daily intake of gluten during the challenge. Sites may also institute a phone or mobile texting plan to remind participants to comply with challenge agent intake and return for follow up visits.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

At the investigator's discretion, participants may self-administer anti-nausea or anti-diarrheal medications (over the counter or prescribed by their own physician) according to the product label as needed. These medications will be recorded.

Listed below are specific restrictions for concomitant therapy:

Systemic anti-inflammatory, immunosuppressive, or immunomodulatory medications, which may include ibuprofen > 2400 mg/day, naproxen >750 mg/day, prednisone >10 mg/day, or methylprednisolone > 8 mg/day.

6.5.1 Rescue Medications and Supportive Care

No rescue medications or supportive care are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

At the discretion of the investigator, the dose of gluten may be decreased to 4 g/day for participants experiencing severe gastrointestinal symptoms (eg, nausea, vomiting, or diarrhea interfering with the participant's daily activities).

In the event that Day 14 procedures are conducted on Day 13, gluten intended for Day 13 will not be consumed.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study site personnel, the Sponsor, and/or designee are not blinded.

6.9 Standard Policies

Not applicable

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9 and 8.11.3.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant interrupts study intervention administration during Days 1 through 3 of the gluten challenge, or for more than 1 day between Day 4 through Day 13 (or Day 12 if endoscopy performed on Day 13) of the gluten challenge.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.

Discontinuation from study intervention is "permanent." Once a participant is discontinued, he/she shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.11. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical decisions must be made by an investigator who is a qualified physician .
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 376 mL for males and 384.5 mL for females (Appendix 8).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 3 months before starting the study.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be allocated, by nonrandom assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Participant will consume the gluten challenge agent daily for 13 days at a total daily dose of 8 g gluten.

At Visit 2, participants will consume 4 g of gluten while at the CRU. The participant will be provided with the remaining amount of gluten for Day 1 of the challenge as well as the gluten for Days 2 to 6 for at home administration. When returning to the CRU on Day 6, participants should bring with them their completed gluten consumption log. The participant will be provided with gluten for Days 7 to 13 for at home administration. When returning to the CRU for Day 14 procedures, participants should bring with them their completed gluten consumption log and any gluten that has not been consumed.

8.1.8.1 Timing of Dose Administration

Participants will be encouraged, but not required, to consume the two gluten doses (total 8 g/day) approximately 6 hours apart, if feasible. Ultimately the timing does not matter to achieve the objectives of the study, but consuming the two doses at different times may limit undesirable gastrointestinal effects for the participant.

8.1.9 Blood Collection

Blood will be collected at Screening, Predose, Day 6, and Day 14 for safety, pharmacodynamic, and biomarker assessments. See Section 1.3 for detailed timing.

8.1.10 Duodenal Biopsy Procedure

After completing the gluten challenge (Day 14), participants will undergo an upper endoscopy (esophagogastroduodenoscopy) with biopsies from the duodenal bulb and distal duodenum. The clinical evaluation of the participants before the procedure will be according to site standard practice. Participants will receive either conscious sedation or medically assisted anesthesia according to PI judgement. Participants will fast for at least 8 hours prior to the procedure. Up to 12 duodenal biopsies, including at least 2 from the duodenal bulb, will be collected using regular biopsy forceps. Four (4) biopsies, including at least one from the duodenal bulb, will be used for histopathological assessment, and the remainder of the biopsies will be used for additional pharmacodynamic and biomarker assessments.

8.1.11 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11.4) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.12 Participant Blinding/Unblinding

Not applicable

8.1.13 Domiciling

Not applicable

8.1.14 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

Not applicable

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below. The total amount of blood to be drawn over the course of the study (from prestudy to poststudy visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 8. The total amount of tissue to be collected during the post-challenge duodenal biopsy study, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body Mass Index (BMI)

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body Mass Index will be rounded to the nearest whole number according to the standard convention of 0.1-0.4 round down and 0.5-0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Participants should be resting in a quiet setting without distractions in a semi-recumbent position for at least 5 minutes prior to having VS measurements obtained.
- Semi-recumbent VS assessments will include systolic and diastolic BP, HR, RR, and temperature.
- Oral or tympanic temperature will be assessed. The same method for measuring body temperature should be used throughout the study for each individual participant.
- BP and HR measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semi-recumbent for at least 10 minutes prior to the ECG measurement during screening.

The correction formula to be used for QTc is Fredericia.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

From the time of intervention allocation/randomization through 14 days following cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered drug-related.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in [Table 2].

Table 2 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1 An overdose of Sponsor's product, as defined in Section 8.5.

2 An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug/challenge agent administered as part of the trial exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

Not applicable

8.7 Pharmacodynamics

8.7.1 Blood and Tissue Samples

Sample collection, storage, and shipment instructions for pharmacodynamic blood (for PBMC and cytokine/chemokine assays) and tissue samples (duodenal biopsy) will be provided in the operations/laboratory manual.

8.7.2 Duodenal Biopsy Pathology

Biopsy sample slides will be sent to a pathologist for review. The pathology report will provide assessments of villus height, crypt depth, villus height/crypt depth ratio, and IEL, which are altered as a result of the pathological effects of gluten on the small intestine.

8.7.3 Celiac Disease Symptom Diary

The CDSD assesses for the presence of symptoms common to CeD over a 24-hour period. See the SoA for the timing of assessments. Symptoms assessed in the diary are diarrhea, abdominal pain, bloating, nausea, and fatigue. Patients who report a symptom are further prompted with 1 to 4 questions to assess severity, duration, frequency, or interference with daily activities. [Canestaro, W. J., et al 2016]

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instructon for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover DNA for future research
- Leftover PBMC samples

8.10 Health Economics Medical Resource Utilization and Health Economics

Not applicable

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Up to approximately 4 weeks prior to intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation.

8.11.2 Treatment Period Visits

Participants will be administered the challenge agent on Day 1 and every day for 13 days. In-clinic visits will occur on Days 1, 6, and 14.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.11.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood samples for PBMCs and cytokines/chemokines are the critical procedure.

All procedures should be completed on the scheduled day per the SoA with the exception of the procedures on Day 14 which may be conducted on Day 13 or 15 if needed for scheduling purposes. If Day 14 procedures will be conducted on Day 13, gluten intended for Day 13 will not be consumed.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

8.11.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose and laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

The pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available pharmacodynamic data. If indicated, these collected samples may also be assayed in an exploratory manner for additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2 - 9.9)

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with Discovery Biology, Translational Biomarkers, and Translational Pharmacology Departments of the Sponsor.

If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

This is an estimation study and no formal hypothesis will be tested. Objectives of the study are stated in Section 3.

9.4 Analysis Endpoints

Primary Endpoints

- Percentage of α-gliadin and ω-gliadin-reactive CD4+ T cells expressing known activation and inhibitory receptors (including but not limited to: CD25 (IL-2R), CD95 (FasR), CD279 (PD-1), TGFβ1R, and IL-27R)) in the peripheral blood before and after gluten challenge and from duodenal biopsies after gluten challenge.

9.5 Analysis Populations

The following population is defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the intervention(s) they actually received.

All Participants as Treated (APT): The All Participants as Treated Population consists of all participants who received low-dose gluten challenge at least for one day. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of intervention, according to the underlying scientific model. Compliance covers such considerations as exposure to intervention (Gluten challenge for Day 1 to 13), availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified by individuals responsible for data

collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one intervention will be included in the Per-Protocol dataset. This population will be used for all primary and secondary sensitivity analyses.

9.6 Statistical Methods

To conduct initial data exploration, summary statistics and plots will be generated as deemed clinically appropriate. For primary endpoint, i.e., the percentages of α-gliadin and ω-gliadin-reactive CD4+ T cells, descriptive summary (mean, standard deviation, median, min, max) will be provided.

In order to assess the association between the primary endpoints and histology (villus height, crypt depth, villus height/crypt depth ratio) with a continuous variable (i.e., CDSD 14-days mean symptoms, CD4+ cell count, etc.), appropriate display such as scatter plot will be provided and correlation coefficient will be reported.

For CDSD, weekly average will be calculated for each patient for both frequency and severity scores of stool (diarrhea and complete spontaneous bowel movement) and non-stool symptoms (abdominal pain, bloating, nausea, tiredness). Then data will be summarized (mean, standard deviation, median, min, max) at the end of each week. In addition, count and proportion of patients who did not indicate diarrhea or constipation (i.e., less than 3 complete spontaneous bowel movements within a 1-week timeframe) will be provided at each time point of interest (Day 7 and Day 14).

9.7 Interim Analyses

No interim analysis is planned for this study.

9.8 Multiplicity

In this estimation study no multiplicity adjustment is planned.

9.9 Sample Size and Power Calculations

Approximately 15 patients will be enrolled in this study. [Table 3] below provides half-width of the 95% CI using t-distribution for selected standard deviation assuming sample size of n=15.

Table 3 Half width of the 95% confidence interval (CI)

n	Standard Deviation	Half width of the 95% CI
15	5	2.7689
15	6	3.3227
15	7	3.8765
15	8	4.4303
15	9	4.9840
15	10	5.5378
15	11	6.0916
15	12	6.6454
15	13	7.1992
15	14	7.7529
15	15	8.3067
15	16	8.8605
15	17	9.4143
15	18	9.9681
15	19	10.5218
15	20	11.0756
15	21	11.6294
15	22	12.1832
15	23	12.7370
15	24	13.2908
15	25	13.8445

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible,

contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in [Table 4] will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit			WBC count with Differential (absolute values): Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/ SGPT	Total Protein
	Glucose fasting	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HLA Genotyping for Celiac Disease • UDS (to include at minimum: amphetamines, barbiturates, cocaine, opiates) • Serology (anti-tTG antibody, HIV antibody, HBsAg, and hepatitis C virus antibody) • Serum/urine β hCG pregnancy test (WOCBP only) • FSH (as needed for women of nonchildbearing potential only) • COVID-19 test			
ALT=alanine aminotransferase; AST= aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HLA: human lymphocyte antigen; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase ; SGPT=serum glutamic-pyruvic transaminase; UDS=urine drug screen; WBC=white blood cell; WOCBP=women of childbearing potential				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

This appendix is not applicable for this study.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d DNA: Deoxyribonucleic acid.

e RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research.

b Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in outlined in the future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the principal investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Conference on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

This appendix is not applicable for this study.

10.8 Appendix 8: Blood Volume and Tissue Collection Tables

Blood Volume

Sample Types Collected	Pre-study	Treatment Period	Total Collections	mL Per Collection	Total mL Per Test
Laboratory Safety Tests	1	1	2	10	20
Anti-tTG/ HIV/ Hepatitis Screen	1	--	1	17	17
Serum β-hCG or serum FSH (females only)	1	--	1	8.5	8.5
Blood for HLA Genotyping for CeD	1	--	1	10	10
Blood for Planned Genetic Analysis	1	--	1	8.5	8.5
Blood for Serum Cytokine/Chemokine Assay	1	2	3	8.5	25.5
Blood for PBMC	1[a] (75 mL total)	2[a] (110 mL total)	3	75 & 110	295
Total Blood Volume per Participant[b]					376 mL for males 384.5 mL for females

hCG=human chorionic gonadotropin ; CeD=celiac disease; FSH=follicle stimulating hormone; HLA=human leukocyte antigen; PBMC=peripheral blood mononuclear cell

[a] Prestudy (Day 1 Predose) sample collection will be 75 mL. Subsequent timepoints (Day 6 and Day 14) will collect 110 mL.

[b] If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (not to exceed 50 mL) may be obtained.

Tissue Collection

Sample Types Collected	Pre-study	Treatment Period	Total Collections	Amount Per Collection
Duodenal biopsy[a]	--	1	1	12 samples

[a] See Operations Manual for details on biopsy collection amounts.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

This appendix is not applicable for this study.

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

   1. The participant may be excluded from the study;

   2. The participant may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

   3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

   OR

   4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

      a. If the repeat test value is within the normal range, the participant may enter the study.

      b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
anti-tTG	Anti-Tissue Transglutaminase
APC	antigen presenting cell
APT	All Participants as Treated
BP	blood pressure
CDSD	Celiac Disease Symptom Diary
CeD	Celiac Disease
CI	confidence interval
CRF	Case Report Form
CRU	clinical research unit
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FODMAP	Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GFD	gluten-free diet
HLA	Human leukocyte antigen
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBS	Irritable bowel syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IEL	Intraepithelial lymphocytes (per 100 enterocytes)
IFN	Interferon
IRB	Institutional Review Board
PP	per-protocol
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
scRNA-Seq	single cell RNA sequencing
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
Teff	effector T cells
Tr1	Type 1 regulatory
Treg	regulatory T cells
tTG	tissue transglutaminase
UDS	urine drug screen
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Anderson, R. P., et al 2000]	Anderson RP, Degano P, Godkin AJ, Jewell DP, Hill AVS. In vivo antigen challenge in celiac disease identifies a single transglutaminase-modified peptide as the dominant A-gliadin T-cell epitope. Nat Med. 2000 Mar;6(3):337-42.	056BMX
[Bodd, M., et al 2013]	Bodd M, Raki M, Bergseng E, Jahnsen J, Lundin KEA, Sollid LM. Direct cloning and tetramer staining to measure the frequency of intestinal gluten-reactive T cells in celiac disease. Eur J Immunol. 2013;43:2605-12.	056BMZ
[Canestaro, W. J., et al 2016]	Canestaro WJ, Edwards TC, Patrick DL. Systematic review: patient-reported outcome measures in coeliac disease for regulatory submissions. Aliment Pharmacol Ther. 2016;44:313-31.	056V6L
[Jabri, B. 2017]	Jabri B, Sollid LM. T cells in celiac disease. J Immunol. 2017;198:3005-14.	056BN0
[Leffler, D., et al 2013]	Leffler D, Schuppan D, Pallav K, Najarian R, Goldsmith JD, Hansen J, et al. Kinetics of the histological, serological and symptomatic responses to gluten challenge in adults with coeliac disease. Gut. 2013;62:996-1004.	056BN2
[Raki, M., et al 2007]	Raki M, Fallang LE, Brottveit M, Bergseng E, Quarsten H, Lundin KEA, et al. Tetramer visualization of gut-homing gluten-specific T cells in the peripheral blood of celiac disease patients. Proc Natl Acad Sci USA. 2007 Feb 20;104(8):2831-6.	056BN3
[Sarna, V. K., et al 2018]	Sarna VK, Skodje GI, Reims HM, Risnes LF, Dahal-Koirala S, Sollid LM, et al. HLA-DQ:gluten tetramer test in blood gives better detection of coeliac patients than biopsy after 14-day gluten challenge. Gut. 2018;67:1606-13.	056BN4

[Tye-Din, J. A., et al 2010]	Tye-Din JA, Stewart JA, Dromey JA, Beissbarth T, van Heel DA, Tatham A, et al. Comprehensive, quantitative mapping of T cell epitopes in gluten in celiac disease. Sci Transl Med. 2010 Jul 21;2(41):41ra51.	056CVW
[Wungjiranirun, M., et al 2016]	Wungjiranirun M, Kelly CP, Leffler DA. Current status of celiac disease drug development. Am J Gastroenterol. 2016 Jun;111:779-86.	056BN5